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TABLE OF CONTENTS

Circular Letters:

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Antimicrobial Action of Terramycin in Vitro and in Vivo: Terramycin is a highly active antimicrobial agent which is effective both in vitro and in vivo against certain of the pathogenic bacteria and certain of the rickettsiae. Studies were carried out to evaluate more extensively the antimicrobial action of terramycin in vitro and its chemotherapeutic action in acute experimental infections in animals.

Partially purified and crystalline terramycin, terramycin hydrochloride, terramycin sulfate, and 2 forms of the sodium salt of terramycin (pH 8.5 and 9.8) were used to determine the sensitivity of various micro-organisms to terramycin. Aureomycin hydrochloride and terramycin hydrochloride were tested simultaneously against a limited series of these micro-organisms, in order to obtain a comparative evaluation. The unit of terramycin has been defined as one microgram of the pure amphoteric compound. The activities of the salts of terramycin are stated in terms of the equivalent weight of pure terramycin. The antimicrobial activity of terramycin in vitro was evaluated by standard methods used for other antibiotics. The method used in this study for determination of the sensitivity of micro-organisms to terramycin was a modification of that previously described by Lenert and Hobby for streptomycin. Tables I, II, and III show the results of the in vitro studies. It appears that

TABLE I.
Antimicrobial Action of Terramycin *in vitro*.

I. Antibacterial Activity of terramycin	Sensitivity: μg of terramycin per cc—37°C			Sensitivity: μg of terramycin per cc—37°C	
Microörganisms	24 hr	48 hr	Microörganisms	24 hr	48 hr
Strep. hemolyticus, Group A			*Bruc. bronchiseptica*	<.3	1.5
C203Mv	<.3	1.5	*H. influenzae* (St.)	2.0	4.0
Type 18	.6	1.5	(DeR.)	2.5	2.5
Strain Br-Mn.	1.5	1.5	*H. pertussis*		5.0†
Strep. hemolyticus, Group C			*K. pneumoniae* (Kin.)	1.5	2.5
Griffith 20	2.5	21.	*K. pneumoniae* (Nol.)	.9	1.5
" 21	.6	1.5	Streptomycin-resistant mutant	21.	21.0*
" 7	.6	.6	*A. aerogenes*	1.5	2.5
H 76	<.3	<.3	Streptomycin-resistant mutant	2.5	2.5*
H 81	.6	.6	Unidentified Gram Neg. Rod (SMR)	5.0	5.0*
D. pneumoniae			*E. coli* (BW 41)	2.5	5.0
I/230, type I	<.02	.02	(W 87)	2.5	5.0
D/39, " II	<.3	<.3	(Bristol)	5.0	5.0
A66, " III	<.3	<.3	*Ps. pyocyaneus* (St.)	5.0	21.
M_3R	<.3	2.5	(ATCC 9027)	21.	21.
BR.	<.3	.5	*Proteus vulgaris*	>167.	>167.
Sch.	<.4	<.4	*S. typhosa* (St.)	1.5	2.5
Strep. viridans (Hawth.)	<.3	2.5	Streptomycin-resistant mutant (NAII)	<.3	1.5*
Enterococcus	.6	.6	Streptomycin-resistant mutant (NAIV)	.6	1.5*
Staph. aureus (H)	.7	1.5	*S. paratyphosa* (Fr.)	2.5	5.0
(Br.)	1.5	1.5	*S. dysenteriae* (Duf.)	2.5	5.0
Staph. albus (Bell)	168.	>168.	*S. typhi murium* (L.I.)	2.5	5.0
C. diphtheriae (No. 210)	.6	.6	*S. typhi murium* (B.I.)	3.0	5.5
Bc. subtilis (W)	.4	.7	*S. newport* (B.I.)	5.5	5.5
(PCI-224)	42.	42.	*S. enteritidis* (B.I.)	3.0	5.5
(No. 6633)	.6	.6	*S. cholera suis* (B.I.)	3.0	5.5
Cl. welchii	<.3	11.			
N. catarrhalis (ATCC)	2.5	2.5			
N. meningitidis	<.3	.5			

* *K. pneumoniae* strain requires 1400 μg streptomycin per cc for inhibition; *A. aerogenes* strain requires 2800 μg; both strains of *S. typhosa* require >5000 μg; and the unidentified gram negative rod requires >100,000 μg of streptomycin for inhibition.

† Readings in this instance were made at 72 hr (37°C).

Table I (Continued)

II. Tuberculostatic Action of Terramycin Hydrochloride:

Microorganisms	Sensitivity: μg of terramycin per cc 5 days—37°C	12 days—37°C	Sensitivity to streptomycin, μg per cc (12 days)
$H_{37}Rv$ (No. 2678)	3.0	13.0	<.5
Freshly isolated strains			
Ni.	3.0	16.0	6.0
Mu.	1.5	26.0	>1000.
Mo.	3.0	13.0	.5
Be.	3.0	26.0	25.0
St.	1.5	26.0	5000.

terramycin is more like penicillin than streptomycin because the action of terramycin is influenced only slightly by environmental factors. As is the case with other antibiotics, however, the concentration of terramycin present influences markedly the rate and extent of inhibition of growth of a given organism. Terramycin is a highly bacteriostatic agent although, under certain conditions, bactericidal action may be apparent. As shown in table 1, it is effective in vitro in low concentrations against a wide variety of microorganisms belonging to both the Gram-positive and Gram-negative groups. The comparative study of the chemotherapeutic activities of terramycin and its salts (table III) indicates that the highly insoluble amphoteric form of terramycin as well as its more soluble salts are all chemotherapeutically effective.

It was found from the studies on animals that terramycin is highly active and capable of protecting mice against infections caused by Streptococcus hemolyticus, Diplococcus pneumoniae, Klebsiella pneumoniae, Hemophilus influenzae, Hemophilus pertussis, Salmonella typhosa, Salmonella newport, Salmonella enteritidis, and Salmonella cholerae suis. It is capable, furthermore, of suppressing temporarily experimental infections in mice caused by S. typhimurium. Limited studies indicate that it may be effective against experimental infections caused by the Clostridia. It is effective when administered by the oral as well as the parenteral routes. Terramycin is not effective in the control of experimental mouse infections produced by Pseudomonas aeruginosa or Proteus vulgaris. Preliminary studies in rats infected with Borrelia recurrentis suggest that 0.82 mg. of terramycin per 100 Gm. of body weight, administered intramuscularly once daily for 4 days, is sufficient to sterilize the blood. Preliminary studies on the chemotherapeutic action of terramycin against experimental mouse

TABLE II.
Antimicrobial Action of Terramycin Hydrochloride: Comparison with Aureomycin Hydrochloride.

	Sensitivity: μg (total wt) per cc	
	Terramycin HCl	Aureomycin HCl (A377)
Strep. hemolyticus (C203Mv)	.9	.9
D. pneumoniae (I/230)	.9	.9
Staph. aureus (H)	.9	.9
K. pneumoniae	2.0	3.5
A. aerogenes	2.0	7.0
E. coli (BW 41)	7.0	14.0
" (W 87)	7.0	14.0
S. typhosa	7.0	7.0
S. dysenteriae	7.0	14.0
S. paratyphosa	7.0	14.0
Proteus vulgaris	450.	>450.
Pseud. pyocyaneus	28.	57.
Brucella bronchiseptica	.9	.9

Tests carried out simultaneously under identical conditions.
Incubation period 48 hr at 37°C.

TABLE III.
Antimicrobial Action of Terramycin: Comparison of the Action of Terramycin and Its Salts.

Organism	Sensitivity: μg of terramycin per cc			
	Terramycin	Terramycin hydrochloride	Terramycin sulfate	Terramycin sodium salt*
Strep. hemolyticus (C203Mv)	5.0	3.0	3.0	3.5
D. pneumoniae (I/230)	<1.5	<1.5	<1.5	<1.5
Staph. aureus (H)	<1.5	<1.5	<1.5	<1.5
Bc. subtilis (W)	<1.5	<1.5	<1.5	<1.5
K. pneumoniae	5.0	6.0	3.0	<1.5
A. aerogenes	5.0	6.0	5.5	3.5
E. coli (BW 41)	11.0	6.0	5.5	3.5
E. coli (W 87)	11.0	6.0	5.5	6.5
Ps. pyocyaneus	42.0	23.0	11.0	26.0
S. dysenteriae	21.0	12.0	5.5	6.5
S. typhosa	5.0	6.0	3.0	3.5
S. paratyphosa	11.0	12.0	5.5	26.0
Proteus vulgaris	>600	>742	>716	>837
Bruc. bronchiseptica	2.5	3.0	<1.5	<1.5
M. tuberculosis				
$H_{37}Rv$ Isolate No. 2678		6.5	6.0	7.5
Freshly isolated strains				
St.		6.5	6.0	4.5
Be.		6.5	6.0	7.5
Mo.		6.5	6.0	
Mu.		4.0	6.0	3.5
Ni.		6.5	6.0	7.5

Except in the case of *M. tuberculosis*, incubation was carried out for 72 hours at 37°C. Cultures of *M. tuberculosis* were incubated for 7 days at 37°C. Longer incubation was not used in view of the fact that the stability of terramycin at 37°C (pH 7.0-7.8) does not permit accurate readings after longer periods of time.

* pH 8.5 sodium salt of terramycin used.

infections produced by Mycobacterium tuberculosis indicate that 7.1 mg. of terramycin per day administered subcutaneously is sufficient to exert a suppressive effect. Terramycin is absorbed rapidly into the circulatory system following oral or parenteral administration. Significant concentrations may be detected in the urine of injected animals in a biologically active form.

Terramycin is a substance of low toxicity. Preliminary studies in mice indicate that at least 375 mg. may be administered orally twice daily for at least 5 days with no untoward symptoms. By the subcutaneous route, 185 mg. per Kg. of body weight may be administered once daily without toxicity. Extensive studies by P'an and his associates in mice and other species of animals further illustrate the low toxicity of this compound.

It is believed that terramycin may prove of value for treatment in certain human infections which are produced by terramycin-sensitive organisms. A therapeutic evaluation of terramycin in human infections has, therefore, been initiated. (Proc. Soc. Exper. Biol. and Med., March '50, G. L. Hobby et al.)

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Terramycin Pharmacologic and Clinical Observations: Studies were conducted to yield information concerning the absorption, diffusion, and excretion of terramycin; and some preliminary clinical trials were made.

In order to determine the terramycin content of various body fluids, the method used by the authors for the determination of aureomycin was used in these studies. Single as well as multiple doses of 1 Gm. of terramycin hydrochloride were administered orally to a number of patients. Single doses were usually given at a time when the stomach was empty. Single oral doses as large as 3 Gm. also were administered to a few patients. Terramycin appears to be readily absorbed. As with aureomycin, detectable amounts have been found in the serum a long time after a single oral dose. Complete disappearance of terramycin activity from the serum occurs at about from 24 to 26 hours after a single dose, although on occasion, a detectable amount still may be present at this time. The concentration in the serum, however, begins to diminish 6 hours or more after a single dose. For this reason, the procedure of giving multiple doses every 6 hours has been adopted. The serum content of terramycin is not significantly increased by increasing the size of the single dose from 1 to 3 Gm., i.e., whatever the size of the oral dose, only a certain amount seems to be absorbed. Large amounts are unabsorbed and pass out in the feces.

The blood serum of patients who are receiving multiple doses of approximately 1 Gm. each by mouth every 6 hours usually contains from 4 to 8 micrograms (µg.) of terramycin per milliliter. After repeated doses, there is a slight tendency for the concentration in the blood serum to increase, although it seems to reach a rather stationary point. The blood serum of patients receiving multiple doses for many days rarely exceeds 8 µg. per ml. In only one case was a higher level obtained; the blood serum was found to contain 16 µg. per ml. Apparently, 1 Gm. of terramycin orally every 6 hours maintains blood serum levels which should be therapeutically effective.

Unlike aureomycin, terramycin appears to be fairly stable in the presence of serum. Several specimens of serum were assayed and left under ordinary refrigeration for 24 hours and then the assay was repeated. The same amount of terramycin was found as had been found on the previous day. Aureomycin had been found unstable even under ordinary refrigeration, and it was necessary immediately to freeze the serum.

Diffusion into Cerebrospinal Fluid. Four patients received 1 Gm. of terramycin hydrochloride every 6 hours for 24 hours prior to spinal puncture. The serum of these patients was found to contain 8 µg. of terramycin per ml. Two additional patients received 1 Gm. of terramycin hydrochloride every 6 hours for 12 hours prior to spinal puncture. The serum of both of these patients was found to contain 4 µg. per ml. Only one of these 6 patients had more than a trace of activity of terramycin in the cerebrospinal fluid; the spinal fluid of this patient contained 1 µg. of terramycin per ml. In one case there was definite evidence of syphilis of the central nervous system in the cerebrospinal fluid; nevertheless, no activity of terramycin was demonstrable in the spinal fluid. It appears, therefore, that, unlike aureomycin, terramycin does not readily traverse the blood-brain barrier.

Diffusion Through the Placenta. Previous studies on penicillin, streptomycin and aureomycin revealed that all 3 antibiotics, when present in the blood of the mother, pass the placental barrier and reach the fetal circulation. Similar studies have been carried out on terramycin. An attempt was made to administer orally at least 2 doses of 1 Gm. each to patients who were in labor. At the time of delivery specimens of the blood were obtained simultaneously from the mother and from the umbilical cord. Terramycin seems to traverse the placenta readily and is available in the fetal circulation.

Pleural Diffusion. Three patients received 1 Gm. of terramycin orally every 6 hours for 3 or 4 doses before diagnostic pleural aspirations were carried out. The levels in the blood serum varied between 2 and 8 μg. per ml. However, antibacterial amounts were found to be present in the pleural fluid in all 3 cases. These findings suggest that terramycin will prove effective in the treatment for infections of the pleural cavity.

Excretion of Terramycin in Bile. Terramycin was found to be excreted readily in the bile; it appears, furthermore, that the substance is concentrated in the liver. Several patients received multiple doses of terramycin by mouth every 6 hours. Blood and fresh bile were collected for the determination of terramycin content. The bile was collected from T-tubes which had been placed in the common bile duct at the time of surgical exploration. The hepatic function in these cases was considered to be normal or near normal.

Excretion of Terramycin in Urine. Fairly large amounts of terramycin appear to be excreted constantly in the urine. Two different types of procedures were employed.

In an effort to determine the amount of terramycin present in the urine at a given time single specimens of urine and of blood were obtained at the same time. Patients in this group were given multiple doses of 1 Gm. of terramycin every 6 hours. Roughly speaking, the higher the level in the serum the greater the concentration of terramycin in the urine. The urine of one patient who had 8 μg. of terramycin per ml of serum contained 512 μg. of terramycin per ml; another patient whose serum contained 4 μg. per ml was found to have 256 μg. of terramycin per ml of urine.

A number of patients were given a single dose of from 1 to 3 Gm. of terramycin. The levels of the antibiotic in serum followed for a 24-hour period varied between 0.5 and 2.0 μg. per ml. In only one instance was the level in the serum higher than 2 μg. per ml. Urine from patients who received single doses of terramycin was collected and pooled in a refrigerator for the 24 hours following the single dose of terramycin by mouth. The urine of these patients contained considerably less than that of those who were receiving multiple doses and in whom higher serum levels of terramycin had been obtained. In this

particular study on pooled 24-hour urine from patients receiving single doses of from 1 to 3 Gm. of terramycin the authors were able to account for no more than 10 percent of the amount administered. To repeat, however, it is evident that freshly voided specimens of urine from patients who have received multiple doses contain rather large amounts of terramycin. Although these findings are of interest, it should be emphasized that the terramycin content of the urine is not an accurate index concerning its therapeutic effectiveness in infections of the urinary tract, and furthermore, these findings give no indication of the tissue content of terramycin.

Excretion of Terramycin in Feces. As was pointed out earlier, it appears that large amounts of terramycin are unabsorbed and are eliminated with the feces. It was not uncommon to find as much as 2.5 mg. of terramycin per ml of feces in patients who were receiving multiple doses of the antibiotic. The high concentration of the drug resulted also in remarkable alteration of the bacterial flora of the feces, similarly to that found with aureomycin and reported by Dearing and Heilman. Preliminary studies in a few cases demonstrated that the feces become odorless and the clostridia, streptococci and coliform bacteria disappear.

Antibacterial Properties. In vitro tests indicate that terramycin has a wide range of antibacterial activity which is similar to that of aureomycin. Some strains of organisms are more sensitive to terramycin than to aureomycin, as was shown in several of the cases the authors report. The Brucellas have been found to be among the organisms most sensitive to terramycin. With the drug incorporated in blood agar the several strains tested were inhibited by from 0.2 to 0.4 μg. per ml.

Preliminary experiments with mice infected with Brucella suis and treated with 0.5 percent of terramycin hydrochloride in the diet indicated that the drug has a considerable suppressive effect on the infection. This effect is comparable to that, which was previously reported by one of the authors (Heilman), of aureomycin. Like aureomycin, however, it did not eliminate all of the organisms from the spleens of the infected mice and its effectiveness was considerably augmented by combination with dihydrostreptomycin.

Clinical Trials. So far, the only satisfactory method of administration of terramycin has been by the oral route. Preparations suitable for intravenous administration are under investigation. As stated previously, the authors have adopted the policy of administering the material every 6 hours by the oral route. From their studies it appears that from 1 to 1.25 Gm. (from 4 to 5 capsules or tablets) is an adequate and effective therapeutic dose. This roughly represents from 4 to 5 Gm. per day for the average adult.

The only untoward reaction encountered by the authors following the oral administration of terramycin is gastro-intestinal irritation, manifested by nausea and on occasion vomiting. This may be troublesome at times. However, the incidence of nausea and vomiting with terramycin is definitely less than with aureomycin. The matter of nausea and vomiting, however, has been almost completely controlled by giving the terramycin with milk. The patient simply swallows one capsule at a time with cold milk rather than water. Milk does not interfere with the absorption of terramycin, as is shown by certain studies on serum content which the authors have carried out on patients receiving terramycin in this fashion.

Preliminary clinical experience with terramycin is encouraging. The results in some of the authors' clinical experience is shown in the table below.

Terramycin: Clinical Trials

Case	Diagnosis	Culture		Daily dose, gm.	Number of days treated	Result
		Source	Organism			
4	Erythema multiforme	—	—	4	13	Bullous type of erythema multiforme. Lesions underwent what was considered fairly rapid involution.
8	Acute laryngo-tracheitis	Throat	Hemophilus influenzae	4	3	Great difficulty in breathing, with inspiratory stridor on admission. Prompt clinical improvement. Recovery.
10	Breast abscess	Fluid, abscess	Micrococcus pyogenes	4	3½	Lesion localized but surgical drainage required in addition to terramycin.
11	Septicemia	Blood	Bacteroides	5 4	13 7	Critically ill patient. Recovered.
29	Acute follicular tonsillitis	Throat	Streptococcus pyogenes	4	3	Prompt clinical response. No fever after 24 hours of treatment.
30	Septic type of sore throat	Throat	Streptococcus pyogenes and Diplococcus pneumoniae	4	7	Very acute edematous throat. Prompt response and recovery.
31	Lobar pneumonia	Sputum	Diplococcus pneumoniae	4	7½	Prompt clinical response.
32	Herpes zoster	—	—	4	7	No demonstrable effect from treatment.
33	Septicemia	Blood	Escherichia coli	5 4	5 4	Prompt clinical and bacteriologic response. Recovery.
34	Urinary infection	Urine	Escherichia coli	4	7	Symptoms promptly subsided. Urine cultures negative.
35	Urinary infection	Urine	Escherichia coli	4	7	Temperature 106° F. shortly after admission. Prompt response. Afebrile in 30 hours. Cultures negative.
36	Pneumonia	Sputum	Usual flora	4	7	No clinical response to 4 days of treatment with penicillin. Prompt response to terramycin. Temperature normal in 36 hours. Recovery.

(Proc. Staff Meet., Mayo Clin., 12 April '50, W. E. Herrell et al.)

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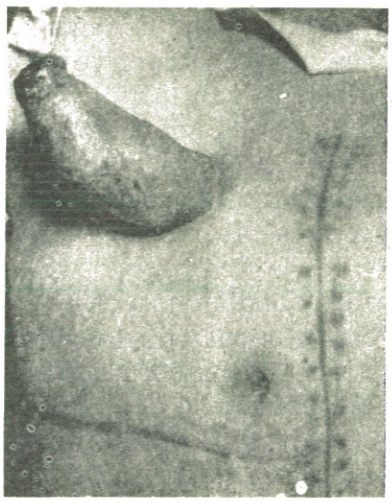
The Management in Polyposis of the Colon: The importance of polyposis (adenomatosis) of the colon is emphasized because it is almost invariably a fatal disease if unrecognized, or if recognized and inadequately treated. Polyposis must be differentiated from multiple polyps arising in chronic inflammatory disease of the colon. This differentiation may be difficult, because similar

clinical pictures may be produced in both conditions and identical end results may ensue. Polyposis must also be differentiated from the very common form of polyps occurring singly or in small numbers. Polyposis is essentially a diffuse disease in which the lesions may be present in great numbers scattered throughout the entire large bowel, or there may be segments which may have either few or not any visible polyps at the time of initial examination; segments apparently uninvolved at one examination may show polyps at a later date.

Polyposis is a familial disease, not related to similar conditions produced by infection or ulceration, and handed down from one generation to another either as mendelian dominants or recessives. It appears that the adenomas do not form until puberty or after and ordinarily become manifest in the second, third, and fourth decades. In the vast majority of cases, malignant degeneration of one or more of the adenomas develops, unless prophylactic measures are employed. Thus it is important to make a correct diagnosis and institute adequate therapy promptly. The disease should always be considered in the differential diagnosis in any condition with diarrhea, and mucus and blood in the stools, particularly when associated with loss of weight and strength. Examination through the sigmoidoscope in cases of polyposis will reveal multiple polyps in the rectum, rectosigmoid or both; x-ray studies with barium and air contrast enemas may give evidence of widespread involvement of the rest of the colon. Biopsy should be made of any polyps within reach of the sigmoidoscope which have an appearance suggestive of malignant degeneration, because the results from such tissue study will influence the choice of procedures taken toward subsequent control of the disease.

In order to avoid the almost certain development of carcinoma in these cases and to establish cure in those in which malignancy is already present, extensive large bowel resection is inevitably necessary. It is the consensus of those who have studied this disease condition that treatment must consist either of (1) colectomy and ileosigmoidostomy (or ileoproctostomy) in combination with fulguration of polyps in the lower segment followed by periodic observation, or (2) resection of the rectum and colon in combination with permanent ileostomy. The authors prefer the latter plan, because fatal carcinomas have been observed to appear at a remote date in the retained rectal or rectosigmoid segment. Furthermore, the skin grafted ileostomy as devised by Dragstedt makes one less reluctant to sacrifice the rectum, because the problems of management incident to the constant skin irritation and mental distress to the patient that occurred with the old standard ileostomy are largely eliminated. The ileostomy of Cattell, the end result of which is a 1-inch stump of bowel protruding above the skin surface, is a step forward but nothing in the authors' experience approaches the Dragstedt type of ileostomy which is illustrated on the next page. With the Dragstedt skin-grafted ileostomy there is direct drainage of ileal contents into a Koenig-Rutzen bag thus avoiding mess and irritation. The dilated distal ileum seems to act as a reservoir like the rectal ampulla with the result that the discharge is not continuous. It seems that the opening through the



View of split thickness skin-grafted ileostomy of Dragstedt type.

abdominal wall produces some valve-like action, and it is noteworthy that the authors' patients have not experienced cramps after about 3 weeks following operation.

Excellent results can be expected if an abdominoperineal resection is done as a first stage, followed in several weeks by colectomy and ileostomy at the second state. The sequence of the resections would be varied, of course, in the presence of evidence of a carcinoma already existing in a segment other than the rectum or sigmoid. In a few instances the entire large bowel has been resected successfully in one stage and although it is desirable to make the period of disability as short as possible, it will probably be found much safer in the great majority of cases to carry out the resection in at least 2 stages.

Guptill has brought to 58 the number of reported cases of patients with multiple polyposis treated surgically by modern methods and to this the authors add 3 cases with a brief summary of each. (Surg., Gynec. and Obst., May '50, R. W. Bartlett and M. E. Peck)

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Antirheumatic Activity of Ascorbic Acid in Large Doses: This preliminary report is offered with the hope of stimulating further investigations of the therapeutic potentialities of ascorbic acid, of its relation to the antirheumatic action of adrenal hormones, and of its possible local role in the tissue reactions of rheumatic fever. Since 2 January 1950, 7 patients with rheumatic fever have been given ascorbic acid by mouth in doses of 1 Gm. 4 times daily (total of 4 Gm. per day), for periods varying from 8 to 26 days. There has been a follow-up period of from 12 days to 2 months in 3 patients in whom therapy has been discontinued; at the time of this writing, 20 March 1950, 4 patients were still receiving treatment. Brief case histories of the 7 patients follow:

Case 1. P. L. is a 13-year-old boy whose pertinent findings prior to treatment included migratory polyarthritis, a temperature of 101° to 102° F. by rectum and elevation of the sedimentation rate. His heart seemed normal except for a slight systolic murmur. Ascorbic acid was given for a total of 8 days (January 2 through January 9, 1950). Within 24 hours of the beginning of treatment the joint manifestations had disappeared, and the fever had lessened. The temperature remained normal after the 2nd day of therapy, but the sedimentation rate continued to be elevated.

Case 2. R. M. is a 14-year-old boy who has suffered for many months from persistent rheumatic fever, severe cardiac involvement and chronic hepatic congestion. Ascorbic acid therapy was begun on February 4, 1950, during a period of increasing rheumatic activity (possibly just a rheumatic-fever cycle), manifested by temperature elevation to 102°F. by rectum, rise in the sedimentation rate and increased congestion of the liver. The fever began to lessen on February 5, and the temperature has remained normal since February 6. The size of the liver has not changed appreciably, and the sedimentation rate is still elevated. Ascorbic acid was given for a total of only 8 days.

Case 3. E. T. is a 15-year-old boy who for 6 weeks prior to therapy had been ill with migratory objective polyarthritis, fever, sinus tachycardia and a rapid sedimentation rate. Except for a slight systolic murmur, his heart seemed normal. With ascorbic acid therapy, which was given for a total of 15 days (February 21 to March 7, 1950), there was prompt improvement in symptoms and reduction in fever. Since the 2nd day of treatment the temperature has been entirely normal, and there have been no symptoms or signs referable to the joints. By March 20 the sedimentation rate had fallen to within normal limits.

CASE 4. W. D. is a 14-year-old boy with rheumatic heart disease whose symptoms of rheumatic fever had been controlled by acetyl salicylic acid. However, after the omission of this drug and prior to treatment with ascorbic acid he had elevation of the temperature to 102°F. by rectum, several nosebleeds and a swollen painful knee. Ascorbic acid therapy was begun on February 22, 1950, and continued to the present time. Improvement was definite but gradual over a 4-day period. He has been symptom-free and afebrile since February 26. The sedimentation rate has fallen from an initial level of 1.4 to the slightly elevated level of 0.55 mm. per minute.

CASE 5. R. F. is an 11-year-old girl who, on admission to the hospital on March 6, 1950, was obviously acutely ill with active rheumatic fever, pancarditis and congestive heart failure. Pertinent findings included a temperature of 104°F. by rectum, tender, swollen finger joints, a respiratory rate of 60 to 75, cardiac enlargement, murmurs of mitral regurgitation and aortic regurgitation, nodal rhythm, a ventricular rate of 160, a pericardial friction rub, marked enlargement and tenderness of the liver, and edema of the legs and lower back. Treatment with ascorbic acid was begun on the evening of March 6. The fever and joint symptoms gradually lessened and have been completely absent since March 13. The friction rub has not been audible since March 10. The cardiac rhythm reverted to normal within 24 hours of therapy, and the heart rate is now about 120. Hepatic congestion and peripheral edema have entirely disappeared. The patient now feels well and appears obviously much improved. The sedimentation rate is still elevated.

CASE 6. A. F. is an 18-year-old boy without cardiac involvement whose rheumatic-fever manifestations just prior to ascorbic acid therapy (given from March 7, 1950, to the present) consisted of elevation of the temperature to 101°F. by rectum, objective polyarthritis and elevation of the sedimentation rate. Treatment was followed by somewhat slow but steady improvement. The temperature has been normal since March 10, and the joint manifestations have remained completely subsided since March 11. The sedimentation rate is still elevated.

CASE 7. P. B. is a 5-year-old boy with known rheumatic heart disease who had a recrudescence of rheumatic fever on March 9, 1950. Manifestations included elevation of the temperature to 104°F. by rectum, sinus tachycardia, pallor and pain and tenderness of the right knee and both ankles. The joint symptoms subsided spontaneously prior to treatment, but the high fever continued. Ascorbic acid therapy was begun on March 14. Since that time there has been a steady decline in temperature, and fever has been entirely absent since March 17. The heart rate has slowed, and the patient's appearance has greatly improved.

Although ascorbic acid is generally considered innocuous, and although no untoward reactions have been encountered in the course of the authors' limited observations, it is believed that there is a need for careful toxicity studies. It is possible that individual doses of more than 1 Gm. or total daily doses of more than 4 Gm., if found harmless, may prove to be therapeutically even more effective.

The mechanism by which ascorbic acid may influence the rheumatic fever disease process is not known, but the large amounts required to produce the apparent effect suggest that it is not a simple matter of replacement therapy. The relation of ascorbic acid to the activity of the adrenal cortex and the recently demonstrated value of adrenocortical activity in the treatment for rheumatic diseases raise many interesting questions concerning the problem of mechanism that cannot be discussed in this short report. The authors emphasize that although their observations suggest that ascorbic acid when administered in sufficient amounts possesses antirheumatic fever activity, no final assessments can yet be made regarding the possible therapeutic value of this substance. Data are as yet insufficient to permit comparison of ascorbic acid with salicylates, cortisone, ACTH and other antirheumatic fever agents. Caution in interpreting apparent antirheumatic effects obtained from combinations of various hormones and ascorbic acid is needed. (New England J. Med., 20 April '50, B. F. Massell et al.)

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Identification of Regional Lymph Nodes by Means of a Vital Staining Dye During Surgery of Gastric Cancer: Although excision of the regional lymph nodes is generally recognized as one of the most important considerations in

the surgical treatment of carcinoma, its accomplishment is often very difficult, or even impossible. For example, the nodes along the internal mammary artery are seldom if ever exposed during a radical mastectomy in the treatment for cancer of the breast.

The regional nodes of the stomach are more accessible than are the nodes of most of the other viscera commonly involved in carcinoma. In cancer of the stomach, the immediate regional or primary nodes are located within the abdomen or near the lower part of the esophagus, all within reach through the exposure required for excision of the stomach. Yet many of the nodes which should logically be removed are seldom seen at operation because of the small size of the nodes and the similarity of their color and consistency to that of the areolar and adipose tissues in which they are enmeshed, and because in many cases, of the inadequacy of the exposure for the identification of some of the nodes such as those in the neighborhood of the celiac axis and the paraesophageal region. In seeking a means of tagging the nodes to make them more easily recognized at surgery, one of the authors recalled Braithwaite's method of mapping lymph nodes in vivo by injecting a dye into the cecal wall and noting its uptake by the nodes which receive lymph from the injected area. This procedure was adopted as a means of identifying otherwise obscure nodes during operations for the extirpation of cancer.

Pontamine sky blue, a dye which gives a deep bright blue color in high dilutions, was adopted. It does not change color within the limits of the acidity and the alkalinity of the body tissues and fluids. Pharmacological tests have shown the dye to be nontoxic. The procedure for use of the dye, as it is now developed, is of such great aid in dealing with actual and potential lymphatic extensions of carcinoma, that the authors have adopted it as a routine procedure in radical gastrectomy.

Dye injections have been made in 34 operations involving the stomach. Twelve of these were cases of carcinoma of the stomach, in 10 of which radical total gastrectomy was performed and in 2, subtotal resection was performed. Six were nonresectable cancerous lesions. Sixteen were gastric ulcers in which local excision of the ulcer or subtotal resection was performed.

With this technic 4 or 5 cc. of a 2-percent solution of the dye is injected into the anterior wall of the stomach as soon as the abdomen is opened and the diagnosis is established. The injections are made near the greater and lesser curvatures of the stomach by means of a Luer syringe of the tuberculin type, fitted with a fine (26 gauge) needle. The dye is instilled into the muscularis rather than into the subserosa, because the muscle tone, contraction waves, and the vascular pulsations in the muscular layer should tend to accelerate the flow of the dye-stained lymph to the regional nodes. The injection is made slowly to minimize puddling of the dye solution at the site of the injection. While the injection is being made, streaks of dye are often observed traversing

small lymph channels on the surface of the stomach and its omental and ligamentous attachments. If staining of one or more of the groups of regional nodes is not seen within the first few minutes, a second injection is made with the same dosage at sites adjacent to the original injections. The authors perform radical total gastrectomy in resectable gastric carcinoma, including a portion of the esophagus and duodenum, the spleen, the greater omentum and the lesser omentum. Subtotal resection is performed only in those cases in which the cancerous involvement is so extensive that the resection can be no more than palliative, or in cases in which the general condition of the patient makes radical total extirpation too hazardous. The extirpation is not started until from 10 to 15 minutes after the injection is completed in order to allow time for the passage of the dye from the stomach to the regional nodes. The severance of the major arteries and veins supplying the stomach is delayed for another few minutes because the major lymphatic vessels follow the blood vessels more or less closely, and too early division of the vessels and their associated lymphatics might interfere with the passage of the dye to the nodes. In the meantime, excessive manipulation of the stomach is avoided in order to minimize the possibility of breaking off particles of cancer tissue into the circulation. Although it might be objected that the delay in dividing major vessels may contribute to the dissemination of cancer during the operative procedure, it is the authors' opinion that the benefit gained by the staining of the nodes more than offsets this hazard. As the dissection proceeds, groups of stained nodes come into view and these, together with neighboring unstained nodes, are included with the specimen which is being removed. Great care is exercised to avoid injury to the hepatic artery and the celiac axis in removing nodes along their course. The entire specimen is removed in a single mass, if possible. After its removal, a careful search is made for nodes which might have been overlooked, particularly along the portal vein, in the region of the common duct and pancreas, and along the remaining lower esophagus.

With their present method of injecting along both curvatures of the stomach, the authors have been able to demonstrate stained nodes in the region of all of the major vessels supplying the stomach, including the right and left gastro-epiploic arteries; gastric tributaries of portal vein; the gastroduodenal, right gastric, hepatic, and left gastric arteries; and the short branches of the lienal artery to the cardiofundic region of the stomach. Nodes have also been identified in the splenic pedicle, along the lower part of the esophagus, over the surface of the pancreas, along the common duct, and along the portal vein. One or more of these groups at times has failed to take the stain, but as the technic has improved, the failures have decreased. If the injection is limited to one or 2 segments of the stomach, the staining of nodes is limited accordingly. With the present method of injecting the muscularis along both curvatures, all or most of the regional groups of nodes receive the dye, and variations in lymphatic patterns become a negligible factor. In some of the cases in which injections have been made with the present technic, there has been no gross

staining of the nodes, and in other cases only 2 or 3 nodes have been stained. It is believed that these failures have been the result of pathologic changes which interfered with the passage of the dye to the nodes. One cause of interference is the blockage of lymph nodes and lymphatic pathways with cancer. The cases falling into this group of failures have had gross widespread involvement of the lymphatics by cancer tissue and have not been considered resectable. In 2 instances, nodes with partial replacement by cancer became stained in the portion not grossly involved with cancer. This seems to indicate that considerable malignant involvement is necessary to prevent the uptake of the dye. This interference does not lessen the usefulness of the method, because nodes which are grossly involved with cancer are usually easily identified by their firmness and color. Several failures have occurred in the cases of benign gastric ulcer in which the dye was injected in the region of the ulcer before the noncancer diagnosis was established. In these cases the nodes either failed entirely to show gross staining, or the staining was limited to not more than several nodes near the site of injection, possibly because of obstruction to the flow of lymph induced by the acute inflammatory changes. However, cancerous lesions are usually not associated with extensive acute inflammation.

A definite handicap in the procedure is the limited time permitted the surgeon for the observation of the uptake of the dye. Although a satisfactory radical total or subtotal gastrectomy requires several hours for its performance, most of the lymphatic pathways have been divided in the first hour or two of the operation. Studies have shown that there is much more extensive and intensive staining after 24 hours than there is after one hour. Although pontamine sky blue has been superior to the other dyes used for intensity and rapidity of the staining of the nodes, it is possible that still other dyes or other technics will give better results than have thus far been obtained. At the present time the authors are experimenting with the addition of hyaluronidase to the dye with the thought that the diffusing properties of the hyaluronidase will accelerate the passage of the dye to the lymph nodes. In the several cases in which it has been used, there has been a speedier and more widespread staining of the nodes than occurred in most of the cases in which the dye alone was used.

Although the procedure described is not yet perfected, it has already been found so useful for the identification and removal of obscure nodes in the performance of radical gastrectomy (as well as in radical operations against cancer in other situations), that it has been adopted in the authors' clinic as a routine procedure in the surgical treatment in those types of cancer in which spread occurs chiefly by way of the lymphatics. (Surg., Gynec. and Obst., May '50, J. Weinberg and E. M. Greaney)

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The Rehabilitation Treatment and Its Rationale in Multiple Sclerosis:

The field of physical medicine affords hope of improvement and maintenance of a higher standard of function to patients with multiple sclerosis.

The aim of treatment in multiple sclerosis must be reasonable rehabilitation in a disease that is considered in most textbooks as an incurable, progressive disease, characterized by exacerbations and remissions, the general trend of the disease being downhill, and eventually terminating in death within from 3 to 15 years.

In order to evaluate critically the results of rehabilitation therapy, it must be determined (1) whether the disability has been practically improved in a sufficient number of cases; (2) whether the degree of improvement (admittedly limited in many cases), balanced against the length of treatment usually required, justifies the effort in view of the anticipated progression of the disease and the possibility of later exacerbation; and (3) whether treatment involving physical activity is detrimental to the disease, is possibly of therapeutic value, or has no effect whatever on morbidity and even mortality.

Since July 1946, the author and co-workers have examined over 390 patients with multiple sclerosis, of whom 287 received rehabilitation treatment. All patients were completely studied with all aspects of their histories evaluated in an attempt to establish possible etiological or aggravating factors; all neurological findings were recorded; full evaluations of disability were made; and all diagnoses were verified by complete laboratory studies, when not done prior to admission.

From data recorded in the cases of 200 patients consecutively admitted, it was found that almost half of the patients, in spite of early disability, were only slightly or moderately disabled even though in many the duration of illness exceeded from 5 to 10 years. In the severe and very severe cases, the age at onset of the illness, the onset of disability residual following onset of illness, and the duration of illness appeared to be of slight significance. Of the 200 cases, 33 percent were not progressive, or had not been so for 5 years or longer; 38 percent were definitely progressive; and in approximately 25 percent, progression was considered to be insidious. In the last group, the vast majority showed evidence, subsequent to treatment, of becoming stationary and most showed improvement, confirming the impression that much of the insidious progress of the disease was the result of disuse.

In a disease of such complex nature as multiple sclerosis, the problems of rehabilitation are numerous and complex.

The neurological involvements observed are tabulated on the next page; in many cases combinations of neurological involvements existed:

Spastic paralysis: paraplegic	24 percent
Spastic paralysis: quadriplegic	62 percent
Cerebellar ataxia: paraplegic	6 percent
Cerebellar ataxia: quadriplegic	43 percent
Position sense impairment: paraplegic	52 percent
Position sense impairment: quadriplegic	10 percent
Visual difficulty (diplopia, blindness, etc.	6 percent

There are difficulties involved in undertaking muscle re-education in a patient with a spastic paralysis combined with cerebellar ataxia, in retraining in cerebellar ataxia complicated by impaired position sense, or in attempting paraplegic brace-crutch rehabilitation with a severe cerebellar ataxia of the upper extremities. In the majority of patients with multiple sclerosis, extreme fatigue is present and impedes rehabilitation efforts. This fatigue is not only of a generalized type, but is specific for individual muscles; a grade 4 muscle can become a zero muscle after from 4 to 8 successive contractions, and recovers to its initial grading only after from 30 to 60 seconds' rest. It has been noted repeatedly that acute emotional upsets may cause aggravation of symptoms. Such upsets may jeopardize rehabilitation achievements; and in many cases, psychiatric support to physical rehabilitation efforts may be required. Regression in ability, believed to ensue as a result of falls, constantly must be considered in the planning of a graduated rehabilitation regimen.

Disuse of muscles probably contributes to the insidious progression of the disease and to its disability. In this series of cases, the occurrence of contracture with disabling limitation of joint motion, making even nursing care difficult, was noted in varying degrees in 60 percent of the patients treated. Scoliosis with cervical lordosis and marked lumbar lordosis, coupled with rotation, all contributing to apparent leg shortening and further motor difficulty were noted in a large percentage of cases.

The most valuable type of rehabilitation in these cases has been intensive muscle re-education of the active resistive type. Increase in passive range by gentle persistent pressure through the various aspects of joint range will usually allow increased active range with increasing amounts of resistance. Rarely is stretch indicated except in the presence of contracture. Never is forceful or abrupt stretching indicated. Any purpose of increasing passive range is for the eventual increase in active range which, in the final analysis, will permit function. Repetition of motion is imperative. Only by achievement of prime movements with increase in range, strength, and endurance can more complex movements eventually be developed. Overcoming the action of spastic muscles can only be maintained by the increased range, strength, and endurance of their antagonists. If the latter is not accomplished, functional passive range of the spastic muscle cannot be maintained. Increase in the volitional control of prime movement facilitates technics of joint stabilization, maintenance of

submaximal contractions, and even voluntary relaxation against gradients of resistance which are ultimately employed in the re-education of ataxia and impaired position sense loss.

No drugs have yet been consistently considered to be a valuable adjunct to rehabilitation therapy.

Prediction of the effects of physical therapy on the eventual mortality in multiple sclerosis will require many years, many patients, suitable controls, and the utmost scrutiny. It is also too early to prognosticate the effect of this treatment on the progressive nature of the disease in cases that were progressive; to judge the maintenance of improvement gained in cases that were classified insidious but in which practical improvement in function was made or to evaluate the maintenance of improvement achieved in patients stationary prior to treatment, because the duration of treatment and follow-up range only from 2 to 4 years. For the present, it may be noted that the vast majority of the patients in this series have made practical improvement and have, in most cases, maintained their improvement during the period they have been observed. An extremely small percentage of patients have had further progression of their disability, although their disease had not previously been definitely progressive, but no patient could objectively be considered to be adversely affected by active physical therapy.

Gross evaluation of results of treatment, based on an observation period of from 18 months to 4 years, may be summarized. Of all the patients treated, 66.0 percent made practical improvement sufficient to justify the duration of the treatment time, to the patient and to the staff. Of the total group, 31.5 percent overcame their major disability. The breakdown of this improvement percentage is significant. Of the mild cases, 80.5 percent of the patients improved objectively and practically, with 57.0 percent overcoming their major disability. Sixty-four percent of the moderately disabled improved objectively, and 18.0 percent overcame their major disability. The severe (capable of but minor self-care) and very severe (totally dependent) patients failed to overcome their major disabilities, but 33.3 percent of the former group and 35.3 percent of the very severe improved in practical function.

In follow-up studies of cases showing improvement, 11 have had subsequent exacerbation with 3 of these experiencing spontaneous remission; all are continuing under a home therapy regimen. Twelve patients have continued to show progress of their disease with subsequent loss of improvement made while under treatment. In all, 81.9 percent of the patients have maintained their improvement, although many had previously been considered progressive. (Occup. Therapy, Feb. '50, R. Cailliet)

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Histoplasmosis - Animal Reservoirs and Other Sources in Nature of the Pathogenic Fungus, Histoplasma: The discovery that Histoplasma capsulatum has a saprophytic development in soil, and that histoplasmosis occurs in certain species of wild and domestic animals, has provided a new method of attack on the problems of the geographic distribution of histoplasmosis and the meaning of prevalent histoplasmin skin sensitivity.

There are two conflicting views concerning the geographic distribution of human histoplasmosis. The occurrence of proved fatal cases of histoplasmosis in many parts of the world clearly indicates a wide geographic distribution of the disease. However, the interpretation that a reaction to the histoplasmin intradermal test in the presence of nontuberculous pulmonary calcification indicates healed benign histoplasmosis, suggests a limited geographic area in which histoplasmosis is prevalent, extending from Kansas City eastward and from southern Iowa and Ohio south through Tennessee. Neither of these views has been resolved, either by the collection of a sufficient number of proved human cases or by laboratory confirmation of the etiologies of the benign diseases which cause nontuberculous pulmonary calcification, although Histoplasma has been isolated from a few persons reported cured at the time of the report. The comparative rarity of proved human cases of histoplasmosis, the difficulties in isolating an etiologic agent from the precalcific lesions of the benign pulmonary disease, the nonspecific nature of histoplasmin, human mobility with consequent exposure of those persons tested to many unknown sensitizing antigens both foreign and local, and our ignorance of how many antigens can sensitize man to histoplasmin, have made a critical determination of the etiology of benign pulmonary calcification difficult.

Determination of whether histoplasmosis is commonly present outside the areas of high histoplasmin sensitivity would aid in interpreting the histoplasmin skin reaction and would help decide whether prevalent histoplasmin sensitivity and pulmonary calcification bear any relationship to human histoplasmosis. The technics of finding human cases of histoplasmosis and of histoplasmin skin testing do not offer easy or early solutions of the problems of geographic distribution and interpretation of histoplasmin sensitivity. The technic of examining suitable species of animals for histoplasmosis by geographic areas may give an answer to both.

In this paper the author summarizes data on the 84 strains of H. capsulatum which have been isolated to date from animals, reports on one new animal host, records 4 additional isolations of H. capsulatum from soil, and discusses the geographic distribution of the isolations from animals and soil by farms within one rural county and by larger areas on a broad geographic basis. Isolations of H. capsulatum from the dog, mouse, brown rat, roof rat, cat, and spotted skunk, have been previously reported. The search for histoplasmosis in animals has been continued in Virginia and Georgia, and to the

end of September 1949, the author and co-workers have isolated H. capsulatum from 5 dogs, one house mouse, 47 brown rats, 4 roof rats, 19 cats, and 7 spotted skunks. In addition to these species, one opossum (Didelphis virginiana) has been found in Virginia with histoplasmosis, the first to be so reported. Following the successful search for histoplasmosis in animals in Virginia and Georgia, similar studies have been made in 3 other localities in Maryland and Texas. These have not yielded infected animals. Failure to find Histoplasma in rats from Baltimore and Towson and from various wild species in Texas may have been due to inadequate samples, faults of technic or the actual lack of infected animals in those areas. Experience in Virginia indicates that the latter explanation is plausible. Data now present do not indicate any seasonal variation.

Experience in the laboratory and the failure to find Histoplasma in animals from certain Virginia and Georgia farms, from Baltimore and from Texas, add emphasis to 3 important considerations in a search for histoplasmosis in animals. One is the necessity for obtaining clean cultures. Because contamination of tissues and cultures by either bacteria or fungi usually inhibits the growth of Histoplasma, it is desirable to bring animals alive to the laboratory, perform the autopsy and make cultures with sterile precautions, at least 5 or 6 from each animal. Cultures from liver and spleen have been most productive. A second conclusion is that among wild animals so far examined in adequate numbers, the rat and the spotted skunk are frequently infected and are, therefore, suitable animals for examination in searching for an animal reservoir of histoplasmosis. Among domestic animals, the cat has been found to be an important host, perhaps because many farm cats catch and eat rats. A third observation has been that the local distribution of infected rats appears to be quite variable. Further studies may show whether the distribution of Histoplasma in nature actually does vary widely and permanently or whether the observations so far made are based on inadequate samples.

The isolation of H. capsulatum has been reported from 2 samples of soil taken from a farm where infected rats had been caught previously. Macroconidia of this fungus were actually demonstrated in the sample after its concentration by flotation. This observation proved conclusively that H. capsulatum has a free-living saprophytic existence in soil. Since this observation was reported, Histoplasma has been found in 4 additional soil samples by inoculating mice with suspensions of soil. Unlike the first 2, these samples had a high organic content. No conclusion concerning the frequency with which Histoplasma grows saprophytically in soil nor the conditions necessary for its growth in this natural medium can be drawn at the present time. More than 400 soil samples have been tested. Although the relationship to human histoplasmosis of the occurrence of the disease in animals and the saprophytic existence of Histoplasma in soil is not understood, it must be concluded that these phenomena are significant in the epidemiology of the human disease. (Am. J. Pub. Health, April '50, C. W. Emmons)

Relationships of Sunlight, Complexion and Heredity to Skin Carcinogenesis: A study was made of a series of 100 consecutive cases of histologically proved skin carcinoma of the exposed surfaces. Because no attempt to adduce further evidence in support of the theory that ultraviolet rays cause cancer of the skin in man was planned and because the study was primarily concerned with the question of what type of skin is most susceptible to cancer of actinic origin, all cases of carcinoma of the covered skin surfaces and of multiple superficial epitheliomatosis were omitted. The sources of the material were the Skin Clinic of the Los Angeles County General Hospital (71 cases) and private practice in the Los Angeles metropolitan area (29 cases). Cases were accepted for this study in the order in which biopsy specimens were reported as basal cell (58 cases), squamous cell (34 cases), or basosquamous cell (8 cases) carcinoma, until the total reached 100.

Although drawn from a regional population which is predominantly brown-eyed, 87 of these 100 patients with histologically proved carcinoma of the exposed surfaces of the skin had eyes of light color, other than brown. In the entire group of 100, 47 originally had dark hair, 25 had hair of medium color, and 28 had light hair, 82 having hair over 50 percent gray at the time of observation. The brown-eyed group of 13 patients consisted of 46 percent female and 54 percent male patients, as against 23 percent female and 77 percent male patients in the blue-eyed group of 87 patients. This might suggest that sunlight may not play as large a part in carcinogenesis in the brown-eyed group as in the blue-eyed group, although about the same percentage of both groups (70 percent and 65.5 percent, respectively) stated that they worked outdoors. The higher incidence of the squamous cell type of carcinoma among male as compared with female patients (39.2 percent in comparison with 19.2 percent) found in this series is comparable to the findings of others. Only 46 percent of the brown-eyed group ever burned, on exposure to sun; 83 percent of the blue-eyed group burned, rather than tanned; 8 percent of the brown-eyed, contrasted with 37 percent of the blue-eyed persons, never tanned. This suggests that sun may not be as important a carcinogenic factor among brown-eyed people as among blue-eyed ones.

It does not appear from this series that ability or inability to tan is a factor determining the histologic type of carcinoma which will develop.

All the lesions on the lower lip and dorsa of the hands were of the squamous cell type. There was a higher incidence of basal cell lesions among the brown-eyed (presumably thicker-skinned) patients than among the blue-eyed ones; this is the reverse of what one would expect. The incidence of multiple carcinomas was much higher in this series than in previously reported studies. In the brown-eyed group, 23 percent had or had had other skin carcinomas; 49.4 percent of the blue-eyed group were so affected. All those having multiple lesions, past or present, had at least one blue-eyed parent (as far as could be determined), and in at least half of this group both parents were blue-eyed.

Furthermore, of the 33 patients in the entire carcinoma group who had 2 blue-eyed parents, 24 had multiple carcinomas of the skin, past or present. These observations suggest that the inheritance of special susceptibility to cutaneous malignant growths may be in some way related to the inheritance of blue eyes or that the inheritance of protective mechanisms against the carcinogenic rays of the sun may be related to the inheritance of brown eyes; a large proportion of those without brown-eyed inheritance (24 of 33, or 73 percent) who had skin cancer had multiple skin cancers by the time they came under observation for this study.

There were only 2 patients in the entire carcinoma group of 100 who had no obvious blue-eyed inheritance; this number represents such a small proportion as to make it commensurate with the incidence of carcinoma of the skin on covered parts of the body, and hence not necessarily related to carcinogenic rays of sunlight. On the other hand, at least 50 percent of the entire series were the offspring of 2 light-eyed parents; the rest had one light-eyed parent. This suggests that eye color has some genetic relation to susceptibility to or protection from light-caused skin carcinoma.

No patient with 2 brown-eyed parents gave a family history of carcinoma of the skin, and only 4 with one brown-eyed parent gave such a history, whereas 21 who gave a family history of carcinoma of the skin had 2 blue-eyed parents. This point adds further weight to the suggestions which were developed in the 2 preceding paragraphs. The lineage of two thirds of the carcinoma group was traced to the British Isles (England, Ireland, and Scotland) although persons with this lineage do not predominate in the population from which this series of cases was derived.

Conclusions. The observations brought forth in this study suggest that the more brown-eyed inheritance a person possesses, the better protected he is from the carcinogenic rays of the sun. Blue-eyed children of blue-eyed parents, are, in general, the most susceptible as a group, but many of these are capable of tanning without repeated burning and thus acquire a fair degree of immunity.

There are certain racial stocks and hereditary complexion patterns in which sunlight is not an important, if any, factor in skin carcinogenesis; these include certainly the Negro and Oriental races, probably the Mexican and Mediterranean and possibly all homozygous brown-eyed persons. Sunlight is by far the most important carcinogenic factor in certain hereditary stocks, when repeatedly encountered in erythema-producing quantities; these include certainly those of Irish-Scotch-English ancestry, probably the blue-eyed North Europeans, including the Scandinavian, and possibly all homozygous blue-eyed persons. (Arch. Dermat. and Syph., April '50, A. F. Hall)

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Follow-up Observations on the Treatment in Bancroftian Filariasis with Hetrazan in British Guiana: Preliminary results of the oral administration of hetrazan to 296 Guianese patients infected with Wuchereria bancrofti have been published. It was found that circulating microfilariae disappeared rapidly during treatment, and that low or negative counts were sustained for from 2 to 4 months after treatment. Clinical improvement occurred during treatment in many patients who exhibited pretreatment filarial symptoms. Monthly follow-up studies which have now been made on many of these patients for periods up to 14 months after cessation of treatment are reported on in this paper.

The observations which have been made demonstrate that the effects produced by hetrazan therapy against the microfilariae of W. bancrofti are not temporary, and suggest strongly that many of the adult worms are permanently damaged or killed by treatment. Although records have not been kept on these patients thus far for periods longer than 14 months, it would be exceedingly difficult to separate any subsequent changes in microfilarial counts or symptoms from the possibility that new infections may have been acquired during the post-treatment period. The maintenance of negative microfilarial counts for 14 months in 60 percent of the patients observed at this period, together with the drastic reduction of microfilariae in those not remaining microfilaria-free is consonant with previous observations made in Puerto Rico, Venezuela, Egypt, Tahiti, and St. Croix. The fate of microfilariae after treatment has started is not well understood, but they do disappear rapidly from the circulation.

The effect of hetrazan against adult W. bancrofti still remains an unsettled question, although considerable indirect evidence denotes that some permanent effect must be produced against mature worms. The localized or general systemic reactions in some patients during treatment suggests the release of filarial protein, with an accompanying allergic response. The occurrence of these localized reactions in body sites which mature worms are known to prefer indicates that something has happened to the worms in these regions which produces a host-tissue response. That this response is much more severe in some patients than in others, is probably related to a variance in sensitivity to whatever substances are released in the process of hetrazan therapy. The variable nature and duration of the response simulates other types of foreign protein reactions. For example, in some patients the only symptom has been a sensation of burning, and the localized tissues became slightly inflammed. In more severe cases, one or more limbs became temporarily swollen, painful to the touch, reddened, and spotted with cutaneous eruptions. General malaise, fever, and sometimes nausea or vomiting accompanied these symptoms. In these Guianese patients, the reactions subsided even though treatment was continued, and in a substantial number of cases partial or permanent relief from pretreatment clinical manifestations was obtained.

The curative effect of hetrazan in patients with clinical symptoms or histories of symptoms is variable. Because the range of dosage administered to the different patients varied considerably and no relationship could be determined between total dosage and the permanence of relief from pretreatment symptoms, it must be assumed that other factors were responsible. (It was observed, however, that total doses of less than 50 mg. per Kg. were not as effective in clearing the circulation of microfilariae as were higher doses.) But the relief obtained from troublesome pretreatment clinical symptoms by a substantial number of these patients throughout the follow-up period does indicate that the curative properties of hetrazan therapy in Bancroftian filariasis must be further investigated. Investigators in Venezuela describe the disappearance of various types of clinical symptoms in 7 out of 10 patients treated with hetrazan, including one with chyluria of several years' duration and the complete reduction of a swollen leg in a young girl. On the other hand, no effect has been produced by hetrazan in cases of elephantiasis studied in Tahitian subjects, and personal correspondence with investigators in several other areas endemic for Bancroftian filariasis has up to the present revealed little or no regression of pretreatment swelling during therapy. The observed variation in the degree of regression of pretreatment symptoms in Guianese patients indicates that all types and stages of filarial symptoms cannot be expected to show improvement during treatment with hetrazan. There is some suggestion that the disease process in the early stages in the course of lymphatic involvement is more likely to be ameloriated by treatment than those in the late stages. Moreover, the recurrence after treatment of troublesome pretreatment symptoms may be influenced by factors other than the presence of living adult worms. For example, in 8 cases of elephantiasis, no microfilariae were present in the circulating blood before treatment and none could be found at any time thereafter. Two of these patients showed partial regressions of swellings during treatment and the remainder obtained no relief whatever. During the follow-up period, 6 patients exhibited filarial symptoms of varying frequency and severity. The absence of circulating microfilariae does not rule out the possibility that living adult worms were present before and after treatment, but possible complications as a result of concurrent bacterial infections must also be considered in these microfilaria-negative patients.

The theory that the cause of elephantiasis in Bancroftian filariasis is lymphatic obstruction by dead worms or their disintegration products, has produced some apprehension in the past concerning after effects which might occur in treated patients if a drug were found to be effective against this parasite. Recent studies have proved almost conclusively that this fear is unwarranted. Patients treated with anthiomaline, neostibosan, and neostam have shown no evidence that elephantiasis was provoked by the death of microfilariae or mature worms. No permanent swellings occurred in 23 Puerto Rican patients treated with hetrazan and followed for 15 months, nor have follow-up observations in Venezuela and St. Croix after hetrazan therapy revealed evidence that

elephantiasis was provoked by treatment. Among 71 of the Guianese patients in this study, 4 showed post-treatment swellings of the hands or arms which persisted for longer than one month; one developed a swelling of the left hand during treatment which persisted for 9 months. In 3 of these cases, the swellings had disappeared at the last examination, and in the remaining 2 they appeared very late during the follow-up period. It is considered impossible to trace the cause of these post-treatment swellings to blockage of the lymphatics by dead worms killed by previous hetrazan therapy, particularly, because all 5 of the patients had exhibited pretreatment clinical symptoms of one sort or another.

No latent after-effects were exhibited in 84 patients who were asymptomatic before treatment and who were followed for from 12 to 14 months after treatment. The reduction in total microfilariaemia within the entire group of 296 patients was greater than 90 percent.

Evaluation of the results in the group as a whole showed that clinical symptoms after treatment varied considerably. Some patients who showed complete or partial relief from pretreatment symptoms during therapy remained free of symptoms throughout the follow-up period and are apparently cured. Others revealed recurrences of pretreatment symptoms with various degrees of frequency after treatment. The number of microfilariae present after treatment, however, seemed to bear no relationship to the presence or absence of symptoms after treatment. It is believed that the sustained absence of microfilariae in a large proportion of the patients treated, together with the complete absence of symptoms after treatment in many cases, demonstrates indirectly that mature worms are permanently affected by treatment with hetrazan. (Am. J. Trop. Med., March '50, R. Hewitt et al.)

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Preliminary Report on the Use of Xylocaine as a Local Anesthetic in Dentistry: Xylocaine was discovered in 1943 by the Swedish chemists Lofgren and Lundquist as a result of a series of experiments with basic anilids which were widely different in structure from the cocaine-procaine group.

Xylocaine is -ω- diethylamino - 2.6 - dimethylacetanilid with the structural formula,

$$\begin{array}{l} CH_3 \qquad\qquad\qquad C_2H_5 \\ \qquad NH - CO \cdot CH_2 - N \\ CH_3 \qquad\qquad\qquad C_2H_5 \end{array}$$

It is not decomposed in strongly acidic or strongly alkaline solutions, or by boiling. The trade product of xylocaine has an osmotic pressure so adjusted that the solution does not cause hemolysis or plasmolysis. Xylocaine seems to be more selective for the sensory and parasympathetic nerve fibers and less specific for the motor nerves. The toxicity manifested locally and systemically is low, compared with other local anesthetics. In the course of study of xylocaine, Gordh has noticed only 2 cases of toxic reactions after deliberate overdosing (1.35 and 3.0 Gm., respectively, as compared with 40 mg. used in dentistry). Among other reactions observed in the course of Gordh's investigation was a transient nausea that occurred after the anesthesia in 2 cases. Otherwise, no noteworthy effects on the pulse, blood pressure, or respiration have been observed. There have been smaller blood pressure falls with xylocaine, with or without epinephrine, than with other drugs. When considerable amounts are injected, the combination with epinephrine should always be used to lessen the risks from reactions. Gordh further reported that in cases in which toxic reaction to procaine and allied drugs had previously occurred, xylocaine can likely be used without such a reaction ensuing. In cases of sensitivity to epinephrine, xylocaine alone may be employed effectively.

Xylocaine is available in 0.5-percent, 1-percent, and 2-percent solutions. At present, the epinephrine ratio ranges are 1:50,000 and 1:100,000. In dentistry the recommended dosage is a 2-percent solution with 1:100,000 epinephrine ratio. In cases in which anesthesia is difficult, a 2-percent solution with 1:50,000 epinephrine is used. However, in most instances the 2-percent 1:100,000 solution is sufficient. Carpules containing 1.8 cc. and 2.4 cc. of solution are supplied for dentistry.

Xylocaine alone, which is far more effective without epinephrine than is procaine, is indicated (1) when there is oversensitivity to epinephrine and when relatively large amounts must be injected in certain conditions in which epinephrine might have a bad effect, such as angiospasm, arteriosclerosis, diabetes, and thyrotoxicosis; (2) in anesthesia of the fingers and toes; and (3) when the surgical treatment called for is very brief.

Xylocaine has been used experimentally in general surgery, urology, otolaryngology, and obstetrics. The commonly employed methods of administering xylocaine are infiltration, conduction, and terminal anesthesia.

The author has used xylocaine in all types of general dentistry in 994 patients. He observed that xylocaine has the following properties as an anesthetic:

1. It clearly excels procaine. This is particularly evident in stubborn cases.

2. It takes effect considerably more rapidly.
3. In infiltration, it is more expansive to adjacent teeth. In mandibular blocks, it is more effective in the premolar area.
4. Local tissue reaction and general side reactions are extremely rare.
5. In contradistinction to procaine, it gives anesthesia effect without the addition of epinephrine.
6. Postinjection reactions are rare.
7. Its selectivity for the sensory and parasympathetic nerve fibers in preference to the motor nerves makes it more comfortable to the patient.
8. In cases of procaine dermatitis, it can be used without reaction.

Many of the author's patients were under psychiatric treatment at the Henry P. Phipps Institute at the Johns Hopkins Hospital. In some instances, when procaine anesthesia had failed (cases including porcelain jacket preparations and cervical procedures in operative dentistry), profound anesthesia was accomplished with xylocaine. There were 14 instances in which the same operative procedure on the same tooth had been attempted without success before xylocaine was employed. The table below shows the results from 994 injections.

METHOD OF INJECTION	TIME OF INJECTION	SYMPTOMS OF ANALGESIA (SECONDS)	ANALGESIA TIME (MINUTES)	ANASTHESIA TIME (MINUTES)	DURATION (HOURS)	NUMBER OF INJECTIONS	SUCCESS OF INJECTIONS	FAILURES	PER CENT OF SUCCESS	SIDE REACTIONS
Infiltration	xx	10	1	2	2	390	379	11	97	nil
Tuberosity and zygomatic	xx	30	1½	3	3	248	243	5	98	nil
Mandibular	xx	30	2	3	3-4	356	346	10	97	nil
Total						994	968	26	97.3	

When the author first started using xylocaine, the 2-percent carpules with epinephrine 1:100,000 were not available. Experiments in mixing epinephrine with xylocaine were conducted. Solutions of 0.5 percent, 1 percent, and 2 percent with epinephrine ratios ranging from 1:10,000, 1:20,000, and 1:40,000 were used. Amounts originally given varied from 1 cc. to 2 cc. It was during this early experimentation that anesthesia failures occurred. Since the prepared carpules of 2-percent 1:100,000 have been employed, there have been no failures.

In only 2 cases was anesthesia a complete failure. The first patient was given 1.8 cc. of 2-percent 1:100,000 solution and, because pain was still present, 2 cc. of 2-percent 1:50,000 solution was given, without success. Failure had also resulted from 2 previous attempts with procaine. The tooth operated upon was an upper canine with an eroded area on the cemental surface at the distal aspect. In the second case, extraction of a lower left third molar, the tooth was extremely tender to percussion prior to extraction and the patient had had

adenitis for 24 hours previous to the extraction. The tooth was very mobile and the patient presented a periodontosis throughout the dental arches. Anesthesia failed with a 2-percent 1:100,000 solution and again with a 2-percent 1:50,000 solution.

In the author's experience, xylocaine without epinephrine is practical routinely only for mandibular injections, 1 cc. of a 1-percent solution being used.

The opportunity for trial in pulp extirpation was presented 3 times during the testing of the drug. In these cases a 2-percent 1:50,000 solution was employed, with excellent results. In the first case presented, a 2-percent 1:100,000 solution of epinephrine was first used. Because pain still persisted, a 2-percent 1:50,000 solution was given and anesthesia was complete.

In experiments with xylocaine by Lloyd and Blythe of the U. S. Marine Hospital in Baltimore, tests were made, in approximately 150 cases, by using procaine on one side and xylocaine on the other side simultaneously. Both infiltration and conduction technics were employed. Their findings show that xylocaine produced anesthesia with greater rapidity and that xylocaine took approximately one hour longer to wear off. In all cases their patients were not informed that an experiment was being conducted. (J. Dent. Research, April '50, L. W. Gruber)

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List of Recent Reports Issued by Naval Medical Research Activities:

Naval Medical Research Institute, NNMC, Bethesda, Maryland.

The Elasticity and Strength of Some Long Bones of the Human Body, 6 October 1949.

Chemical and Radiochemical Studies of the Distribution of Gallium in the Organism, 20 October 1949.

The Effect of Breathing Oxygen at 2.5 Atmospheres on the Rate of Elimination of Carbon Monoxide in Man, 21 November 1949.

Changes in Weight and Ascorbic Acid Content of the Adrenals in Guinea Pigs Infected with Pneumococci, 23 November 1949.

Responses of Human Subjects to Immersion in Ice Water and to Slow and Fast Rewarming, 23 March 1950.

The Sulfonamides as Factors in Increasing Susceptibility to Parasitic Invasion, 18 April 1950.

Naval School of Aviation Medicine, NAS, Pensacola, Fla. and Kenyon College of Gambier, Ohio.

Loudness of Speaking: The Effect of the Intensity of Side-Tone Upon the Intensity of the Speaker, 30 September 1949.

Naval School of Aviation Medicine, NAS, Pensacola, Fla. and The Ohio State University Research Foundation, Columbus, Ohio.

Some Effects Upon Voice of Hearing Tones of Varying Intensity and Frequency While Reading, 25 January 1950.

Naval School of Aviation Medicine, NAS, Pensacola, Fla. and The Tulane University of Louisiana.

Post-Rotational Perception of Apparent Bodily Rotation, 3 February 1950.

Vertigo Incidence Among Naval Aviators, 15 March 1950.

Naval Medical Field Research Laboratory, Camp Lejeune, North Carolina.

Design of an Easily Stacked, Lightweight Durable Hand Dipper for Mosquito Survey, 17 March 1950.

Preliminary Studies on Photobiological Action and Photodecomposition by Ultraviolet Irradiation at Low Temperatures, 6 April 1950.

Evaluation of Reading Efficiency of Marine Corps Personnel, 19 April 1950.

Naval Medical Research Unit No. 3, Cario, Egypt.

Taste Reactions to Antithyroid Substances, 20 March 1950.

Note: Those interested in seeing copies of the complete reports should address their request to the research activity from which the report originates.

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Military Medicine and Surgery Program at AMA Meeting: The Session on Military Medicine and Surgery at the meeting of the American Medical Association in San Francisco (26-30 June) will be held on Wednesday and Thursday mornings, 28 and 29 June. It is expected that each section will begin at 9:00 a.m. However, the exact time, as well as the building and room locations will appear in the official AMA program.

For Wednesday Morning, 28 June

TIME

1. MILITARY MEDICINE AND SURGERY AS A SPECIALTY..... 15 min.

By Rear Admiral L. T. Boone, MC, USN, General Inspector of Medical Department, United States Navy

Discussants

Dr. H. A. Rusk
Associate Editor, New York Times; Professor and Chairman, Dept. of Rehabilitation and Physical Medicine, New York University

Dr. I. S. Ravdin
John Rhea Barton Prof. of Surgery, Hospital of the University of Pennsylvania

2. MEDICAL PROBLEMS ENCOUNTERED IN A-BOMB EXPLOSIONS..... 15 min.

By Brigadier General J. P. Cooney, MC, USA, Chief Radiology Branch, Division of Military Application, United States Atomic Energy Commission

Discussants

Dr. A. H. Dowdy
Prof. of Radiology and Chairman, Dept. of Radiology University of California School of Medicine

Dr. S. Warren
Director, Division of Biology and Medicine, United States Atomic Energy Commission

3. TREATMENT OF HIGH INTENSITY THERMAL BURNS.....15 min.

By Dr. E. I. Evans, Professor of Surgery and Director, Laboratory of Surgical Research, Medical College of Virginia

Discussants

Dr. J. B. Brown
Assoc. Prof., Clinical Surgery, School of Medicine
Washington University

Major E. J. Pulaski, MC, USA
Chief, Surgical Research Unit
Brooke Army Medical Center

4. THE TREATMENT OF RADIATION INJURIES..... 15 min.

By Dr. J. G. Allen, Associate Professor of Surgery, University of Chicago, School of Medicine

Discussants

Dr. S. L. Warren
Dean, School of Medicine
University of California

Lt. Comdr. E. P. Cronkite, MC, USN
Head, Hematology Facility
Naval Medical Research Institute

5. STRESS AS A FACTOR IN THE PRODUCTION OF NEURO-PSYCHIATRIC DISEASES..... 15 min.

By Dr. D. W. Hastings, Professor and Head, Department of Psychiatry and Neurology, University of Minnesota, School of Medicine

Discussants

Dr. F. R. Hanson
Associate Prof. of Psychiatry
McGill University

Dr. D. A. Boyd, Jr.
Consultant in Psychiatry
Mayo Clinic

6. CIVILIAN DEFENSE PLANNING..... 15 min.

By Dr. N. C. Kiefer, Director, Health Resources Division, National Security Resources Board

Discussants

Dr. J. C. Sargent
Chairman, Council on National Emergency Medical Services
American Medical Association

Dr. R. H. Flinn
Medical Director
Health Emergency Planning
US Public Health Service

For Thursday Morning, 29 June

TIME

7. MEDICAL PROBLEMS IN CHEMICAL WARFARE ..... 15 min.

By Colonel J. R. Wood, MC, USA, Chief, Medical Division, Army Chemical Center

Discussants

Dr. F. C. McLean
Prof. Physiology
University of Chicago

Dr. G. M. Lyon
Special Assistant for Atomic Medicine and Chief, Radioisotope Section, Department of Medicine and Surgery Veterans Administration

8. MEDICAL RESEARCH AND DEVELOPMENT IN THE ARMED FORCES ..... 15 min.

By Major General G. E. Armstrong, MC, USA, Deputy Surgeon General, United States Army

Discussants

Dr. L. T. Coggeshall
Prof. of Medicine and Chairman, Dept. of Medicine; Dean, Division of Biological Sciences, University of Chicago

Dr. A. C. Ivy
Head, Dept. of Clinical Science and Vice President of University of Illinois

9. MEDICAL PROBLEMS ENCOUNTERED IN UNDERSEA CRAFT... 15 min.

By Rear Admiral H. L. Pugh, MC, USN, Deputy Surgeon General, United States Navy

Captain O. D. Yarbrough, MC, USN
Director, Submarine Medicine Div
Bureau of Medicine and Surgery

Dr. H. T. Karsner
Medical Research Advisor to Bureau of Medicine and Surgery

TIME

10. COMMUNICABLE DISEASE PROBLEMS IN THE ARMED FORCES DURING PEACE AND WAR..... 15 min.

By Dr. J. E. Smadel, Director, Department of Virus and Rickettsial Diseases, Army Medical Department Research and Graduate School, Army Medical Center

Discussants

Dr. N. Topping
Associate Director
National Institues of Health
Public Health Service

Dr. H. A. Reimann
Professor of Medicine
The Jefferson Medical College
of Philadelphia

11. THE EFFECTS OF AIR TRANSPORTATION ON CLINICAL CONDITIONS: ANALYSIS OF 16,000 CASE REPORTS IN 1949... 15 min.

By Lt. Colonel B. A. Strickland, USAF, MC, Chief, Department of Air Evacuation, and Dr. J. A. Rafferty, Chief, Department of Biometrics, USAF School of Aviation Medicine

Discussants

Brig. Gen. W. H. Graham, USAF, MC
Surgeon to the President
and Special Assistant to
The Surgeon General, US Air Force

Dr. W. R. Lovelace II
Head, Lovelace Clinic
Albuquerque, Mex
New Mexico

12. MILITARY MEDICINE AND ITS RELATION TO AMERICAN MEDICINE ..... 15 min.

By Dr. R. L. Meiling, Director of Medical Services, Office of the Secretary of Defense

Discussants

Maj. Gen. G. E. Armstrong
Deputy Surgeon General, US Army

Rear Adm. C. A. Swanson
The Surgeon General, US Navy

Maj. Gen. H. G. Armstrong
The Surgeon General, US Air Force

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BUPERS CIRCULAR LETTER 50-49 7 April 1950

To: All Ships and Stations

Subj: Medical Internship and Residency Policy

1. The following memorandum from the Secretary of Defense is quoted herewith for information and guidance of all concerned:

10 March 1950

Memorandum for The Secretary of the Army
The Secretary of the Navy
The Secretary of the Air Force

Subj: Medical Internship and Residency Policy

1. In the interest of obtaining maximum uniformity, economy, and efficiency in the operation of the professional training programs in the armed forces, and upon the recommendation of the Director of Medical Services, the following policies and standards are established for the resident and intern programs for physicians of the medical services of the three military departments:

a. Participation in internship programs shall be limited to individuals who, in their written requests for such internships, volunteer for and agree to serve minimum periods of active duty in the armed forces in accordance with the following options:

	Active duty including Internship
(1) For military internship in a military hospital (effective with internships commencing 1 January 1951):	
(a) One year of internship	2 years
(b) Two years of internship	4 years
(2) For military internship in a civilian hospital	
(a) One year of internship	3 years

b. Armed forces interns in military and civilian hospitals will be required satisfactorily to complete 8 months of internship prior to becoming eligible to participate in professional examinations leading to appointment in the Regular service.

c. Eligibility to compete for residency training in an armed forces program will be limited to medical officers of the Regular service with selection criteria on the following priority basis:

(1) Regular service officers completing 2 or more years of commissioned service, exclusive of internship.
(2) Regular service officers with 1 to 2 years of commissioned service, exclusive of internship.
(3) Regular service officers with less than 1 year of commissioned service, exclusive of internship.
(4) Armed forces interns contingent upon appointment in Regular service in accordance with directives.
(5) Civilian interns contingent upon appointment in the Regular service in accordance with directives.

d. Participation in residency training programs shall be limited to Regular service officers who in their written requests for such residency volunteer and agree to serve for periods of active duty in the armed forces in accordance with the following options:

	Active duty including Residency
(1) For military residency in a military hospital:	
(a) One year of residency	2 years
(b) Two years of residency	4 years
(c) Three years of residency	6 years
(2) For courses or military residency in a civilian school or hospital:	
(a) Six months to 1 year of training	3 years
or residency	3 years
(b) Two years of residency	5 years
(c) Three years of residency	7 years

e. Periods of active duty for which a medical officer has volunteered under the Armed Forces Intern and Resident Programs respectively are separate periods and may not be served concurrently. However, this will not preclude medical officers from entering residency training prior to completion of the volunteer periods of active duty including internship indicated in paragraph 1.a. above; provided that this service is completed following the active duty including residency indicated in paragraph 1.d.

f. Resignations or requests for release from active duty received from officers who have voluntarily accepted periods of active duty hereinbefore mentioned will not be favorably considered, except for convenience of the Government, until total periods of applicable volunteer service have been completed.

g. Applications for internship or residency training accepted prior to the date of this memorandum are not affected by these changes but will be

governed by previously existing regulations of the department concerned.

2. It is directed that the above policies and standards be implemented.

Louis Johnson
--BuPers. F. W. McMahon, DCNP.

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Additional Letter Added to List in BuMed Circular Letter 50-44: BuMed Circular Letter 45-250 has been officially added to the list of canceled circular letters contained in the original BuMed Circular Letter 50-44, dated 26 April 1950 (page 27, Navy Medical News Letter of 5 May 1950).

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BUMED CIRCULAR LETTER 50-41a Joint Letter 21 April 1950

From: Chief of Naval Personnel
Chief of the Bureau of Medicine and Surgery
Commandant of the Marine Corps

To: Commanders, All Naval Training Centers
Commanding Generals, U. S. Marine Corps Recruit Depots, Parris Island, S. C., and San Diego, Calif.

Subj: Procedure for Disposition of Enlisted and Inducted Recruits with Disqualifying Physical Disability Existing Prior to Initial Enlistment or Induction in the Naval Service.

Ref: (a) Career Compensation Act of 1949 (Public Law 351 - 81st Congress)
(b) SecNav Regulations and Instructions, dtd 16 Nov 1949, for administration of Title IV of reference (a)
(c) SecNav ltr of 7 Feb 1950, Item 50-91 NDB 15 Feb 1950
(d) BuPers-BuMed-MarCorps Joint Letter of 24 Feb 1949 - Subj: Procedure for Disposition of Male Enlisted and Inducted Recruits and Authority to take Final Action on Aptitude Board Reports (BuMed C/L 49-19), appd by SecNav 24 Feb 1949

Encl: (1) Prescribed waiver form

This directive establishes procedures for the early separation from the Naval Service of any member without prior active Naval Service as defined in

section 412 of reference (a), and who has served less than six (6) months on active duty in his initial enlistment or induction in the Naval Service, and who is considered to be unfit for Naval Service by reason of physical disability which is not the proximate result of the performance of active duty.

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BUMED CIRCULAR LETTER 50-45 5 May 1950

From: Chief, Bureau of Medicine and Surgery
To: All Naval Hospitals and All Stations having a Representative of the Medical Department Aboard

Subj: Storeroom Values of Standard Medical and Dental Supplies and Equipment Available for Use, NAVMED-1311 (1-50)

Ref: (a) BuMed CirLtr 49-138
(b) Revised Hospital Accounting Instructions (NAVMED P-1296)

1. Reference (a) is hereby canceled. Subject form replaces the temporary form enclosed with reference (a) and is now available at the district publications and printing offices.

2. All stations with a representative of the Medical Department aboard shall submit NAVMED-1311 quarterly with the NAVMED-E.

3. The "Analysis of Supplies and Equipment Available for Use" report required from naval hospitals by reference (b) is hereby canceled. The sample "Analysis of Supplies and Equipment Available for Use" form shall be removed from the appendix of reference (b) and replaced by subject form. NAVMED-1311 shall be submitted quarterly with other financial reports.

4. Instructions for the preparation of NAVMED-1311 are printed thereon.

C. A. Swanson

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BUMED CIRCULAR LETTER 50-46 5 May 1950

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations

Subj: Medical Department Money Allotments for Ships, Fiscal Year 1951

Refs: (a) BuMed CirLtr 49-46; N.D. Bulletin of 30 Apr 1949, 49-311
(b) BuMed CirLtr 45-178; AS&SL Jul-Dec 1945, 45-801, p. 342
(c) BuMed CirLtr 48-26; AS&SL Jan-Jun 1948, 48-165, p. 155
(d) BuMed CirLtr 48-143; N.D. Bulletin of 15 Dec 1948, 48-938
(e) BuMed CirLtr 49-103; N.D. Bulletin of 31 Aug 1949, 49-612
(f) BuSandA Manual, Vol. III, Para. 36001 (4) and Appendix A, Para. 4(c)

This letter, which appears in full in the 15 May Navy Department Bulletin, contains information and instructions concerning medical and dental stores for all ships.

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BUMED CIRCULAR LETTER 50-47 5 May 1950

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations

Subj: Functioning of Clinical Boards

Ref: (a) BuMed CirLtr 50-22; 15 March 1950, N.D. Bul., 50-163

This letter, which appears in the 15 May 1950 Navy Department Bulletin, contains a modification of the enclosure with reference (a).

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BUMED CIRCULAR LETTER 50-48 9 May 1950

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations to which are Attached Hospital Corps Personnel on Duty Independent of a Medical Officer

Subj: Reference Books for Hospital Corps Personnel on Independent Duty

1. In order to make available appropriate reference material for Hospital Corps personnel on duty independent of a medical officer, contracts have been let for the purchase of the textbooks listed. The Bureau will send these books to addressees:

a. Manual of Medical Emergencies, by S. C. Cullen and E. G. Gross
b. Nursing in Clinical Medicine, by Julius Jensen and Deborah Maclurg Jensen
c. First Aid, Surgical and Medical, 5th ed., by Warren H. Cole and Charles B. Puestow
d. A Course in Practical Therapeutics, by Morton Emil Rehfus

2. A receipt card will be included with each shipment. Upon delivery, the Medical Department representative shall sign the receipt card and return it to the Bureau of Medicine and Surgery, Attention: Code 25.

3. There will be no charge against current allotments for these books, but the Medical Department of the receiving activity will be responsible for accounting for them.

C. A. Swanson

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BUMED CIRCULAR LETTER 50-49 9 May 1950

From: Chief, Bureau of Medicine and Surgery
To: District Medical and Dental Officers
Inspector, Naval Medical Activities, Pacific Coast
Inspectors, Naval Dental Activities, Atlantic Coast and Pacific Coast
Commanding Officers, Naval Hospitals and Dispensaries

Subj: Implementation of Naval Shore Establishment Survey Board Recommendations

Ref: (a) CNO ltr Op-08/OK Ser 24P08 of 15 Mar 1950 to distribution list, regarding subject

1. Reference (a) provides that the local representatives of Navy Department bureaus and offices shall assist the district commandants in the implementation of the recommendations made by the Naval Shore Establishment Survey Boards. The local representatives of the Bureau of Medicine and Surgery should continually assist the appropriate local District Commandant (or Air Training Command) on pertinent Medical Department matters in the continuing survey and evaluation of shore facilities and personnel required to support the peacetime Navy.

2. Each addressee is requested to familiarize himself with the status of the subject surveys in his district. It is requested that a copy of any suggestions or recommendations made by the District Medical or Dental Officer to the Commandant (or Air Training Command) be forwarded to the Bureau.

3. Any such recommendations made shall give consideration to reductions in medical and dental facilities embodied in current programs of the Secretary of Defense and Office of Medical Services. These programs, and previous actions taken as a result of the Survey Board recommendations, will be evaluated to determine (a) if medical and dental facilities are adequate to support the Operating Forces at the level provided in the Navy's current budget, and (b) if they are sufficient to provide for the initial stages of mobilization. Recommendations involving these factors, such as are accepted by the Chief of Naval Operations and Secretary of the Navy, will, in case of conflicts with

Defense Department programs, be submitted to the Secretary of Defense through appropriate channels. C. A. Swanson

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BUMED CIRCULAR LETTER 50-50

Subj: Central Facilities Provided for the Department of Defense by Armed Forces Institute of Pathology

This letter, to which a date has not been given, is a joint letter of the Army, Navy, and Air Force. It consists of about 25 pages. In the Navy, it will be distributed to all holders of the Bulletin of BuMed Circular Letters.

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BUMED CIRCULAR LETTER 50-51

This letter, to which the exact subject and date have not been given, will concern the cancellation or modification of certain Medical Department directives and procedures made necessary by the release of joint Army, Navy, and Air Force letter above (BuMed CirLtr 50-50).

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BUMED CIRCULAR LETTER 50-52 10 May 1950

From: Chief, Bureau of Medicine and Surgery
To: All Stations within the Continental United States

Subj: Care of the Dead when Death Occurs Away from a Station having a Contract

Ref: (a) Paragraph 341.1, Manual Medical Department, 1945
(b) Paragraph 341.6, Manual Medical Department, 1945

1. Reference (b) provides that "When death occurs in the continental United States away from a naval command, the dispatch forms prescribed in paragraphs 341.1 and 3418 shall be modified to conform with the circumstances. Item (j) of paragraph 341.1 shall include information as to the location of the body, the name and address of the person having custody, and, if known, the wishes of the next of kin as to disposition. The dispatch to the next of kin (par. 3418) shall be appropriate to the circumstances. Unless death has occurred at the home of the deceased, the form of dispatch to the next of kin shall be altered only by elimination of the information regarding the furnishing of the escort. Upon receipt of instructions as to disposition desired, the Bureau will arrange either through the nearest naval activity or through a

local civilian undertaker for preparation and encasement of the remains at a cost not to exceed $200, with proper shipping instructions. An additional amount not to exceed $75 (par. 3447.1) may be allowed to apply to funeral expenses at final destination."

2. This Bureau has recently experienced several embarrassing situations in handling remains in cases such as those covered by reference (b). The duty stations of the individuals concerned in these particular cases contacted the nearest naval activity to the place of death and issued instructions rather than complying with reference (b). This Bureau not knowing of this action and assuming charge of the case in accordance with the regulations proceeded to issue instructions relative to preparation, encasement, and disposition in accordance with reference (b). The information and instructions issued by this Bureau proved to be in conflict with action taken by the duty stations and, therefore, reflected very badly on this Bureau and the Navy Department as a whole.

3. In view of the foregoing and in order to facilitate efficient and expeditious disposition of remains in cases of this nature, it is requested that after initial instructions contained in references (a) and (b) have been complied with that no further action be taken in order that the Bureau of Medicine and Surgery may assume charge and arrange for preparation, encasement, and disposition in accordance with reference (b). In the event it is deemed necessary by the duty station to issue further instructions, the Bureau of Medicine and Surgery should be made an information addressee of the communication. C. A. Swanson

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NAVY DEPARTMENT
BUREAU OF MEDICINE AND SURGERY
WASHINGTON 25, D. C.

OFFICIAL BUSINESS

Permit No. 1048
NavMed-369

PENALTY FOR PRIVATE USE TO AVOID PAYMENT OF POSTAGE, $300